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Susceptibility of PharmChek™ Drugs of Abuse Patch to Environment Contamination

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The PharmChek Drugs of Abuse Patch was evaluated for contamination by low microgram quantities of cocaine, methamphetamine, and heroin from outside the patch (contamination from without, CFWO) and inside the patch, on the exterior skin (contamination from with, CWFI). To study CFWO, patches were first saturated with artificial sweat and attached to clean Petri dishes. Exposure of the outer membrane of the patch to drugs in mildly basic solutions showed increasing levels of drugs inside the patch over time. Drugs must be uncharged to pass through the exterior of the patch. Drugs applied in acidic, artificial sweat (pH 4.7), where most drugs are positively charged, resulted in little or no CFWO in the patch. Sweat Patches exposed to drug vapors revealed virtually no CWFO when both the pad and the patch exterior were dry; however, the patch cantained significant drug concentrations when the pad was moistened with artificial sweat and the patch exterior membrane was moistened with either artificial sweat or tap water. In vivo experiments, testing CFWI, showed positive patch test results when drugs were placed externally on the skin before the patch was applied, despite normal hygenic washing, passage of time (up to six days), and swabbing with 70% isopropanol.

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1. Introduction

Ingested drugs have long been known to appear in sweat (see Kidwell *et al.*[1] for review), and a number of sweat collection devices have been developed to facilitate drug detection.[2],[3],[4],[5],[6],[7],[8],[9] Generally, sweat collection devices sandwich an absorbent pad between the skin and an outer membrane using a tamper-evident adhesive backing on the membrane. Careful preparation of the skin prior to application of the patch helps reduce the possibility of bacterial growth and previous skin contamination. Newer, non-occlusive membranes allow water vapor to pass through the membrane, which increases comfort for the wearer and allows longer-term wear.[10]

Sudormed, Inc. has married the non-occlusive membrane with a collection pad to produce a sweat collection patch marketed by PharmChem, Inc. as the PharmChek™ Drugs of Abuse patch (referred throughout the text as the sweat patch or patch). It has found wide application in the criminal justice system due to perceived advantages including user friendliness, non-invasiveness, easily observed placement and removal of the sweat patch, detectable adulteration attempts, long drug-use detection interval during the wearing of approximately one week, and potential to identify unique metabolites. In addition, there are reports that the sweat patch may either deter or cause individuals to be more forthcoming about drug use.[11],[12]

Two seemingly attractive features of the sweat patch are: 1) the skin is "cleansed" before application of the patch, potentially removing previously deposited drugs and 2) the patch appears to protect the skin from contamination by the external environment after being applied. These attributes have focused the scientific community's recent attention to the sweat patch.[12],[13],[14],[15]

The manufacturer claims that "passive exposure to ambient drugs of abuse during the wear period is not detected by conventional toxicological analysis of post-wear patches."[10] More forcefully, a representative of the manufacturer stated, "The patch is carefully designed so that contaminants from the environment cannot penetrate the adhesive barrier from the outside, and therefore the patch can be worn during most normal activities (bathing and swimming, for example) without affecting the integrity of the test."[11] Despite these assertions, it is reasonable to ask whether contamination on the outside of the patch (external contamination from without, CFWO) could affect the reliability of results.

Researchers have not thoroughly studied this issue but have stated: "Nonvolatile substances from the environment cannot penetrate the transparent film, a semipermeable membrane over the pad that allows oxygen, water, and carbon dioxide to pass through the patch, leaving the skin underneath healthy."[12] and "Larger nonvolatile molecules that cannot pass the polyurethane layer remain trapped on the collection pad.[13] and "The transparent film portion of the patch allows oxygen, carbon dioxide, and water vapor to escape but prevents the escape of nonvolatile constituents present in sweat."[14] An additional account states, "... molecules larger than vapor-phase isopropanol are excluded by the molecular pore structure (~2 nm) of the plastic membrane.[15] Skopp *et al.*[16] used the dye rhodamine B to study the permeability of the sweat patch's polyurethane membrane from CFWO. No CFWO was observed with rhodamine B. Unfortunately, the dye they chose is hydrophilic, with both amine and carboxylic acid functional groups. This zwitterion would be charged at the pH of their experiment (pH 7.4) and would not be expected to penetrate the membrane readily. Furthermore, the state of hydration of the inner pad is not reported. If it was dry, that would also reduce transport of

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molecules and give a false impression of impermeability. Cone, *et al.* explored CFWO by exposing subjects wearing skin patches to cocaine vapor. They observed some unexpectedly, high concentrations of cocaine (greater than 200 ng per patch), but dismissed them as laboratory handling error "because other patches collected from the same subject under similar conditions were determined to be negative."[14] Furthermore, subjects wore light clothing to cover the patches and were not actively sweating, factors which are predicted to lessen CFWO.

Other than CFWO, one may ask whether false positive results may arise from the prior presence of drugs on the exterior of the skin, not removed by the cleaning process (external contamination from within, under the patch, CFWI). CFWI is distinct from the process where drugs permeate the skin in areas not covered by the patch, enter the blood stream, and are re-excreted in sweat into the patch. Except in extreme cases of external contamination, this is unlikely to occur because, generally speaking, drugs do not enter the bloodstream through skin in high concentrations (see below). For CFWI to be observed, only a source of drugs, a plausible transfer mechanism to the skin, and binding of the drugs to the skin need occur. Because most individuals tested for drug use by the patch are previous drug users, their environment is more likely to be contaminated with drugs, increasing the likelihood that their skin will contact drugs from prior drug using episodes. Because the skin is "cleansed" using 70% isopropanol swabs before application of the patch, it was thought that prior drug exposures of the skin should not affect the results. Our previous research showed that 70% isopropanol does not remove all the drug deposited on the skin.[17] Thus, the very people most likely to be tested by the sweat patch are also the most likely to be externally contaminated.

The sweat patch is becoming increasingly used in the U.S. criminal justice system to monitor drug use during pretrial and probationary release. Recently, offices of the U.S. Federal Public Defender have described cases where individuals under supervised pretrial or probationary release have had their sweat patch test positive while denying drug use in a credible manner.[18] Cases include individuals with urine negative/patch positive, or close contact with a drug-contaminated environment. Several of these cases involved individuals identified as methamphetamine positive, who denied vehemently any methamphetamine use, some even while admitting they used other illegal drugs. In at least one instance, consecutive 48-hour urine specimens (covering the length of wear of the patch) tested negative while the patch tested positive. A common thread running through these cases was that the individuals were in environments where profuse sweating was commonplace and, frequently, tested positive for drugs with which they had a prior use history (and possible environmental contamination).

This paper explores some of the variables affecting how drugs from the external environment can enter the patch, tests cleaning human skin after the contamination with known amounts of drugs, and the persistence of drugs placed on skin. Improvements are proposed in the design and use of the sweat patch that may reduce CFWO plus reduce and detect CFWI.

2. Materials and methods

2.1 Analysis

Skin swabs or sweat patch pads were placed in a 15-mL plastic test tube, held in place mechanically by a permeable divider at the upper third of the tube, then spiked with deuterated internal standard in isopropanol, and dried. The swabs were washed with three 2-mL portions of 0.1 M hydrochloric acid which was separated by brief centrifugation after each addition. The aqueous extracts were applied to MP1 solid phase extraction column (Ansys, Inc.) using a Zymark Rapid Trace. The columns were conditioned with methanol and 0.01 M hydrochloric acid prior to the sample application and then rinsed with 0.01 M hydrochloric acid and 20% aqueous acetone. The columns were dried under positive pressure for three minutes and the drugs were eluted with 50:10:1 methylene chloride:isopropanol:ammonium hydroxide. The eluate was concentrated to dryness under a stream of nitrogen and mixed with 70 µL 0.1% triethylamine in methylene chloride, 50 µL acetic anhydride, and 20 µL pentafluoropropanol then heated for 30 minutes at 70°C. The excess derivatization reagents were evaporated under a stream of nitrogen; the drugs were reconstituted in 20 µL of ethyl acetate and 2 µL aliquots were injected into a Varian Saturn 4 GC/MS. The derivatization procedure converts all morphine and 6- or 3-acetylmorphine to heroin. Thus, the degradation of heroin cannot be determined by this procedure. The GC parameters were as follows: 30m DB-5MS (J & W Scientific) column, initial temperature 100°C (12 seconds) ramped at 18°C/min to 280°C then 5°C/min to 300°C and held at 300°C for 2.9 min. for a total run time of 17.1 min. Samples were ionized using isobutane chemical ionization. Two mass ranges were scanned; *m/z 90 to m/z* 300 for the amphetamines and *m/z* 150 to *m/z* 450 for BE, cocaine, and heroin. Quantitation was performed by ratioing the peak areas of the protonated molecular ions to their respective deuterated internal standard. The limit of detection, calculated statistically from a series of blanks, varied from run to run and was approximately 2 ng/specimen. The extraction conditions for removing the drugs from the pads were different than recommended by the manufacturer which used 80% methanol:acid. While this organic solvent would remove lipophilic materials such as THC (not analyzed by our procedure), it would also extract lipids arising from the skin, which could interfere with the analysis.

2.1.1 Formulation of artificial sweat

Artificial sweat was formulated in accordance with the 3160/2 ISO standard as reported by Randin[19] and Skopp *et al.*[20]. Briefly, the artificial sweat contained 20 g/L NaCl, 17.5 g/L NH_4Cl, 5 g/L acetic acid, and 15 g/L *d,l* lactic acid. The pH was adjusted to 4.7 using NaOH.

2.1.2 Recovery of drugs from patches

Experiments were done in triplicate. Artificial sweat (1mL), containing nominally 100 ng of cocaine, BE, heroin, amphetamine, methamphetamine, and MDMA was place on a pad. The pad was placed on a petri dish and allowed to dry at 37°C for 3 hr. The patches were then extracted and the drugs quantitated. The average recoveries were: cocaine, 81%; BE 76%, heroin, 85%; amphetamine, 107%, methamphetamine, 88%; and MDMA, 83%.

2.2 Drug contamination on skin experiments

Before contamination with drugs, the skin of the volunteer was pre-swabbed twice with sterile, 70% isopropanol skin swabs (at t = 0) for 20 seconds per swabbing, wearing new, disposable, powder-free latex gloves, and the swabs saved for analysis. Then, specified quantities of d_0 drug standards (10 µg or 500 ng in ethanol containing 100 - 400 ng rhodamine 6G dye for visualization with UV light) were placed on upper arm skin locations. In addition, some d_0 drug standards (10 µg) were placed on the upper arm skin in artificial sweat and dried. The artificial sweat took far longer to dry and was thus less convenient. Urine specimens were collected *ad librium* for six hours after contaminating four and five skin areas with a total of 40-50 µg of drugs, then each sample analyzed. After normal activities and hygiene (including shower), the dry skin was swabbed twice (manufacturer recommends only once) with 70% isopropanol swabs using new latex gloves and saved for analysis. Then patches were applied to previously drug-contaminated skin areas following the patch manufacturer's instructions except that the skin was "clean" twice.[21] Sweat patch pads were removed for analysis according to manufacturer's instructions as well, at the designated time intervals. After patch removal, the skin was wiped for 20 sec. with alcohol swabs. All alcohol swabs plus internal standard were analyzed by the same procedure as pads from the sweat patches.

2.2.1. Patches applied simultaneously, then removed sequentially

To evaluate the effect of increased time and sweating on the concentrations of CFWI in the patch, both upper arm areas (left and right) were contaminated in two areas per arm with drugs simultaneously as described above. The next day, after normal hygienic shower, each (left and right) upper arm area was swabbed twice with 70% IPA swabs, and allowed to dry. Patches were applied to the four CFWI areas. Patches were removed at 30, 105, 210, and 2880 min. After removal, the area under each patch was swabbed with 70% IPA and the four swabs saved for analysis. Results are from one subject, who exercised vigorously after patches are presented.

2.2.2. Patches applied sequentially, then removed sequentially

To evaluate the effect of increasing time before the patches are applied on the concentrations of CFWI in the patch, both (left and right) upper arm areas were contaminated with drugs simultaneously (day 0) as described above. The next day (day 1), after normal hygienic shower, one CFWI area of upper arm was swabbed twice with 70% IPA, and allowed to dry. A patch was applied to the CFWI areas. Similarly, this patch application procedure was repeated on day 2, day 3, day 4, and day 6. Patches were removed after three days (on days 4, 5, 6, 7, and 9) and analyzed. After removal, the area under each patch was swabbed with 70% IPA and the (4) swabs saved for analysis. Results are from one subject, who exercised vigorously after patches are presented.

2.2.3. Equilibrium of drugs in the patch

To evaluate the stability of drugs in the patch and equilibrium with the skin, 500 ng of d_0-drugs in 0.1 mL ethanol were placed in duplicate on the skin and dried. Sweat patches were immediately applied. In addition, the same amount of drug was placed on patches in duplicate, dried, and the patches placed on the skin. After a 2.5 day interval, the patches were removed and analyzed. Moderate exercise was undertaken during this time.

2.3 Drugs placed on exterior of patches attached to Petri dishes
2.3.1 In liquid solutions

PharmChek™ patches moistened with artificial sweat were attached to Petri dishes previously cleaned with alcohol swabs. Drug solutions (10 µg target concentrations of cocaine, heroin, and methamphetamine/0.1 mL) in artificial sweat (pH 4.7) or 0.1 M sodium bicarbonate (pH 8.3) were deposited on the exterior surface of the patch prewarmed to 37°C. After incubating for approximately 0, 1, 5, 15, 30, 60, and 120 min at 37°C, the exteriors of the patches were flushed vigorously with tap water for 30 sec to stop any further diffusion and reduce the chance of inadvertent contamination by drugs during removal of the pad. Pads were removed according to the manufacturer's instructions, internal standard applied, and analyzed as described above.

2.3.2 Exposure to cocaine and methamphetamine vapor

The pads of the sweat patches were either pre-moistened with 1.0 mL artificial sweat or left untreated (dry) then attached to cleaned Petri dish lids. Artificial sweat (300 µL), 0.1 M aqueous sodium bicarbonate (300 µL) or tap water (300 µL, pH 7.3) were placed on the exterior membrane of those pads pre-moistened with artificial sweat. The sweat patches attached to Petri dishes were placed in a chamber measuring 30 x 30 x 35 cm. Free-base cocaine (9.4 mg) and methamphetamine (4.7 mg, from methamphetamine-HCl+NaOH) were heated until vaporized inside the chamber. After exposure, the patches on Petri dish lids were flushed vigorously with tap water for 30 sec. Pads were removed according to the manufacturer's instructions, internal standard applied, and analyzed as described above.

Two additional patches were constructed using the same membrane as the sweat patch and a filter paper pad approximating the size of the sweat patch pad. One patch contained an air pocket between the pad and the external membrane, held apart by a plastic screen (*ca.* 6 mesh). Both patches were wetted with artificial sweat within and outside (artificial sweat/artificial sweat) before placement in the drug vapor chamber.

2.4 Degradation of methamphetamine by bleach.

Varying amounts of commercial bleach solution (5, 10, 20, 40 µL) were added to 1000 ng of methamphetamine in 1 mL of distilled water to test conditions under which methamphetamine may be converted to amphetamine. The solution was heated to 37°C for 30-45 minutes, cooled, deuterated internal standards added, made acidic with 0.1M HCl, and extracted. In some experiments, 0.1 M aqueous bicarbonate, artificial sweat, or 0.1 M aqueous hydrochloric acid were substituted for the distilled water. The different media did not appear to dramatically affect the oxidation results.

2.5 Lactic acid assay

A commercially available assay for lactic acid (Sigma Diagnostics®, Sigma-Aldrich Co., St. Louis, MO, USA) in serum was adapted for use with swab and sweat patch extracts. The reagent was reconstituted in 10 mL water according to the package insert, then 0.2 mL was placed in wells of an ELISA plate. The first row of 8 wells were reagent blanks, used for "zeroing" the spectrometer. Standards of *d,l-*, *d-*, and *l-* lactic acid were prepared in the laboratory and serially diluted to the range of 2 - 300 µg/mL (expressed as *d*-lactic acid for the

standard curves) in 0.1 M hydrochloric acid. Standard curves were prepared by adding 20 uL aliquots to ELISA plate wells containing 0.2 mL test reagent. Aqueous extracts of specimens were aliquotted in the same manner. The plate was mixed on a rotating table for 10 min then the absorbance measured using the #6 filter on a TiterTeck Multiskan MCC/340. The assay's limit of quantitation was approximately 2 µg/mL. This assay does not detect *d*-lactic acid. Control experiments with *d*-lactic acid showed that it does not convert to *l*-lactic acid under the extraction conditions and that *l*-lactic acid is stable. The range of concentrations for *l*-lactic acid from the patches was 50-2000 µg/patch with most being in the range of 500 µg/patch. The range of concentrations for the swabs was 16-260 µg/swab, with the higher values reflecting swabs obtained after the patch was removed. The average extraction efficiency for *l*-lactic acid from the patches was 84% (using spiked patches).

3. Results and Discussion

3.1 Diffusion experiments (CFWO)

As part of the U.S. governmental regulatory approval process, the sweat patch developer included in its FDA 510(k) clearance documentation a study to support impermeability of the polyurethane membrane of the sweat patch.[22] In this study, blank patches were fortified with 37.5 ng cocaine, benzoylecgonine, methamphetamine, heroin, morphine, codeine, marijuana (THC), and phencyclidine (PCP), air dried, and placed on Petri dishes. A test set was immersed in tap water at 39°C for 24 h and the patches analyzed. The reported recovery is shown in Table 1.

Table 1 - Recovery of Drugs from Immersed Patches. Data from.[22]

Drug or metabolite	% Recovery
cocaine	80
benzoylecgonine	103
methamphetamine	88
heroin	88
morphine	98
codeine	99
THC	86
PCP	88

Impermeability of the membrane should not be inferred from the data given in Table 1 because most of the recoveries were below 100%. In a real-life setting, drug concentrations on the surface of the pad may be arbitrarily large. Using these experimental results as a guide, it would require only 200 ng of drug on the surface of the patch to produce 20 ng (the current,

commercial cut-off level[23]) on the interior pad, if 10% of the drug (corresponding to a 90% recovery) permeated the membrane. Furthermore, in the experiment described, the pads inside the patches were dry before immersion, which would reduce drug transport (see below) and the low concentrations of drugs used would slow diffusion. Rather than measuring permeability, this experiment measured short-term stability of drugs in dry patches (dry being unrealistic for patches on human skin).

Theoretically, for materials to permeate a membrane which is not microscopically porous, the material must have some solubility in the membrane. Most drugs of abuse are ionically charged at physiological pH. Because the polyurethane membrane protecting that patch would be less polar than water, charged species should be relatively insoluble in this membrane and the diffusion reduced or eliminated. However, at higher pHs, most drugs of abuse are neutral and, therefore, their solubility in the polyurethane membrane and diffusion through the membrane would increase. After the drug diffuses into the membrane, it must diffuse out for the drug to appear in the patch. Otherwise, the membrane would act as a concentration device similar to that in solid phase microextractions[24] and no CFWO would be observed. An aqueous layer inside the membrane more acidic than the pKa of most nitrogen containing drugs (generally greater than 7) will facilitate this transfer because the drug becomes protonated on the inside of the membrane and then becomes less soluble in the membrane compared to the media in the pad. Sweat is normally acidic or neutral; therefore, as long as the individual is actively sweating the pad inside the patch would become saturated with sweat and promote diffusion of drugs and CFWO.

We expanded and repeated experiments measuring permeability of the patch. For example, Fig. 1 shows how rapidly drugs penetrate the membrane from the outside when placed in slightly basic media such as sodium bicarbonate (pH 8.3). Note that the pH of the bicarbonate solution is similar to the acid dissociation constants of cocaine (pKa 8.4 to 8.69)[25] and heroin (pKa=7.6)[26] but substantially lower than methamphetamine (pKa=10.1)[26]. A substantial proportion of cocaine and heroin are in the free base form and much less for methamphetamine. Solubility in the membrane of even the free base form of the drug may account for the observed penetration of only 17% (at most) of the applied drug. Nevertheless, the commercial cut-off level of 20 ng/patch[1] would be reached within 5 min for all the drugs.

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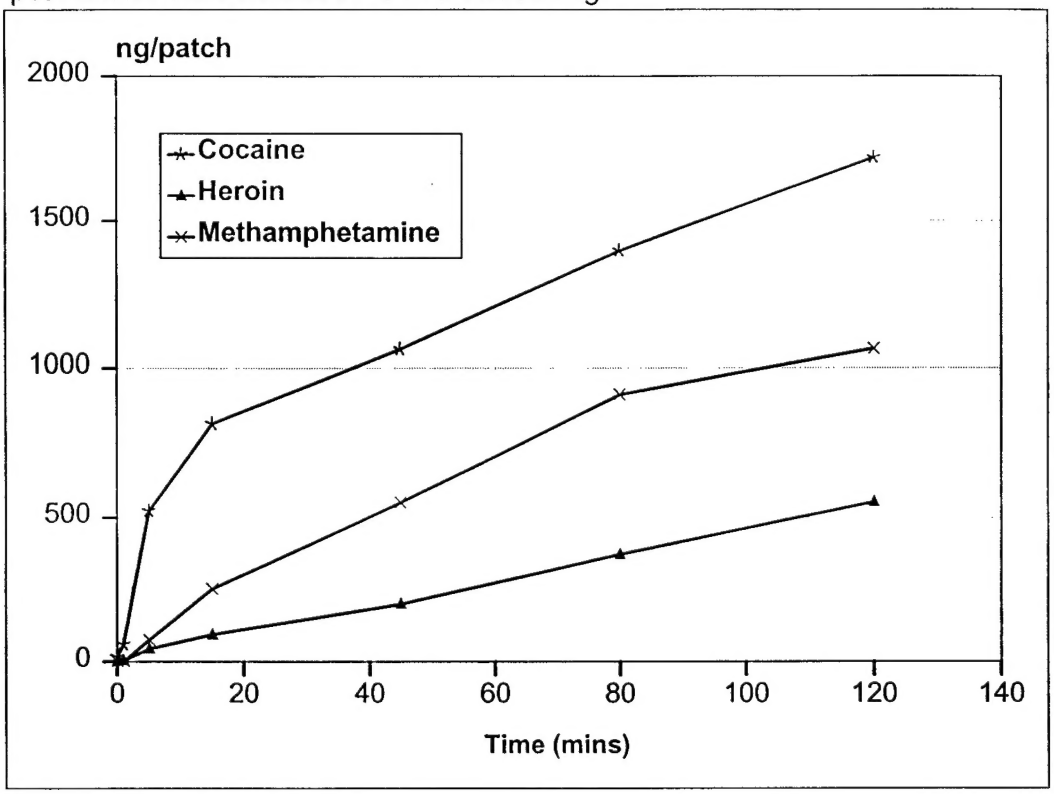
[1]10 ng/mL of a 2 mL extract.

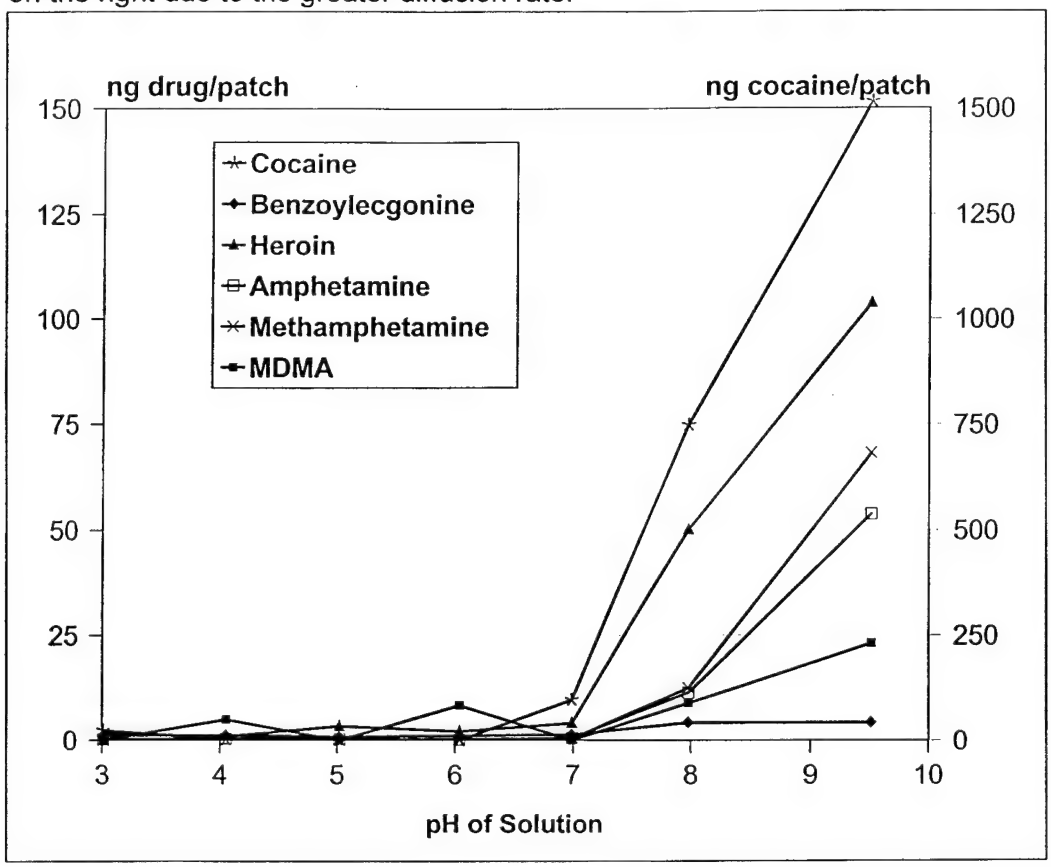
Figure 1 - Diffusion of drugs placed on the outside of patches. Patches were applied to petri dishes and 10 µg of cocaine, heroin, and methamphetamine were place on the exterior in 300 µL of 0.1 bicarbonate. The petri dishes were held at 37°C in a sealed bag.



The diffusion of dyes through the membrane was also evaluated. Rhodamine B (1 mg/mL in 0.1 M carbonate buffer) and fluoresceine (1 mg/mL in 0.1M phosphate, pH 5) readily passed through the membrane into the patch when the patch was wet with 0.1M bicarbonate. Substantial color was observed after incubation overnight at 37°C. Rhodamine 6G and crystal violet (both in carbonate buffer) had much less diffusion. Potassium hydroxide only passed slightly through the membrane as judged by wetting a patch with valeryl bromocresol purple in water and observing the cleavage of valeric acid and the production of the purple color of bromocresol purple in the presence of base.

Figure 2 shows the effect of pH on the diffusion of drugs through the polyurethane membrane. As expected, as the pH becomes more acidic, less drug is transferred through the membrane, reinforcing the necessity of the drugs being uncharged for facile diffusion. Methamphetamine and amphetamine, having higher pKas than cocaine or heroin require a higher pH for rapid diffusion.

Figure 2 - Diffusion of Drugs at Various pHs. The patches were wet with artificial sweat, applied to petri dishes, and exposed to a mixture of 10 µg of each drug in 0.1 M phosphate buffer at 37°C for 30 min. The scale for cocaine is on the right due to the greater diffusion rate.



Application of the drugs in artificial sweat rather than bicarbonate solution showed little diffusion into the patch because the pH of the sweat was adjusted to pH 4.7, as suggested in the literature.[20] The pH of sweat varies, with reported values from pH 6.2 - 8.2 among male and pH 6.1 - 6.5 among female college students exercising in a gymnasium.[27] Other reports found mean sweat pH of 5.82 (σ = 0.68) for 8 men and 6.78 (σ = 0.60) for 8 men when the sweat was stimulated by pilocarpine.[28] Studies also found that lower rates of sweating caused the pH to be lower due to higher rates of lactic acid secretion; however as sweat flow increases, the sweat pH turns alkaline due to bicarbonate secretion.[28] In the case of apocrine sweat, its pH is usually more basic than eccrine sweat because it contains higher ammonia concentrations.[28] Soaps and shampoos used in normal washing and bathing can affect skin and sweat pH, and range in pH from mildly acidic to the more basic pH 10.[29]. The pH of 4.7 for artificial sweat (use in these experiments) may be too low for a test solution as this pH came from literature primarily concerned with the corrosion of metals worn on or touched by the human body.[19],[30] Higher pHs would be expected to allow greater diffusion of drugs.

3.1.2 Exposure to cocaine and methamphetamine vapor

To test the effect of vapor deposition, state of hydration, and pH of hydration on CFWO, sweat patches (wet or dry) were attached to Petri dishes, placed in a chamber, and exposed to static vapor of cocaine and methamphetamine (Figure 3). The entry of drugs through the sweat patch membrane and into the pad appears to be facilitated by aqueous media. When a dry sweat patch containing a dry patch pad was contaminated with cocaine and methamphetamine vapor, virtually no drugs penetrated the patch membrane. On the other hand, when the sweat patch pad was saturated with artificial sweat and its external membrane wetted with either artificial sweat, bicarbonate buffer, or tap water, substantial amounts of cocaine (447, 843, and 588 ng respectively) and methamphetamine (30, 74, and 87 ng respectively) entered the patch pad. These results show that vaporized methamphetamine and/or cocaine can cause CFWO when patches are wet.

Due to the limited number of samples and experimental difficulties in controlling vapor deposition over a large area, no attempt was made to test wether or not the drug concentration was uniform over all the patches. However, the pattern of dry outside/dry inside vs. wet outside/wet inside is clear. Water facilitates the movement of molecules through the polyurethane membrane of the sweat patch. Thus, the experiments conducted by Cone *et al.*[14] where they exposed individuals wearing sweat patches to crack smoke cannot be compared to these results for two reasons. First, the individuals were not likely to be actively sweating (because the subjects resided indoors, in a temperature controlled environment); therefore, little if any liquid would have been present inside or outside the sweat patch. Second, the main goal of Cone *et al.*[14] was to study passive *ingestion* of the cocaine, passage through the body, and excretion back into /through the sweat. Their experimental design called for protecting the sweat patches with clothing. This would even further reduce drug deposition on the surface of the potentially dry patches.

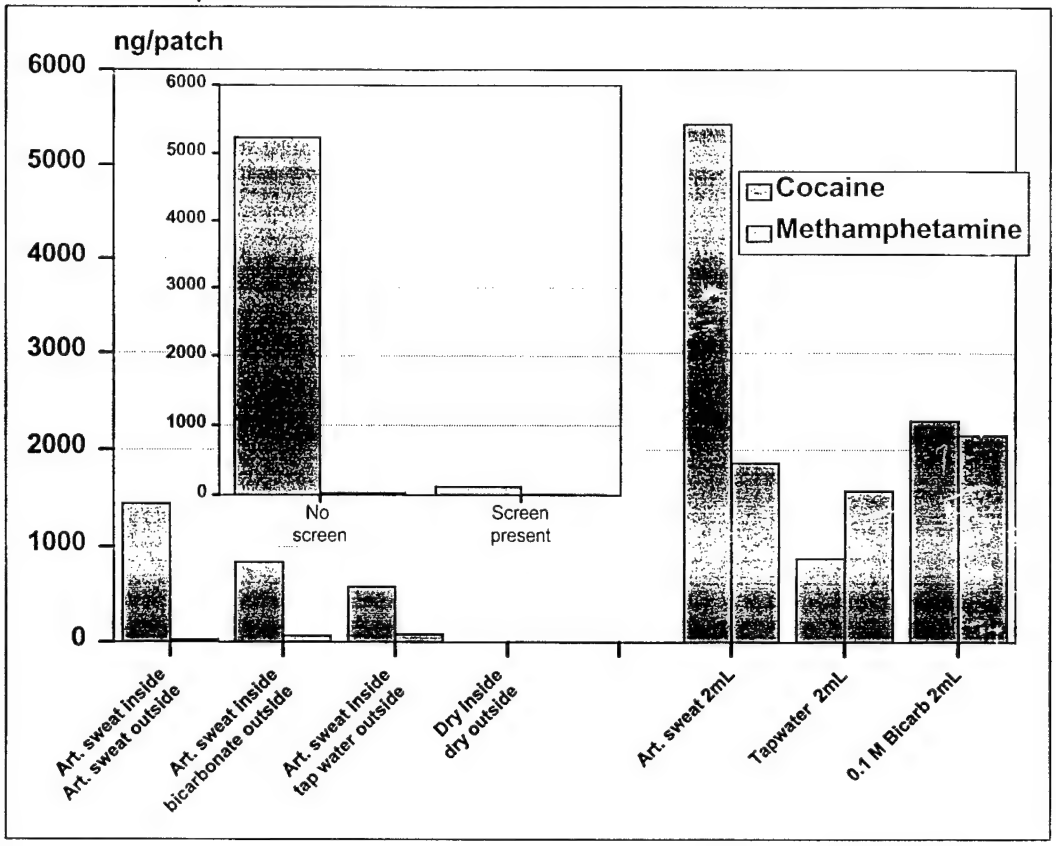
A larger than expected relative concentration of cocaine (compared with methamphetamine) appeared in the sweat patch containing artificial sweat inside and outside (compared with the sweat patch containing artificial sweat inside and bicarbonate buffer outside). The acidic pH of artificial sweat, in theory, would maintain the charged state of the cocaine molecule, making it more difficult to permeate the membrane. One possible explanation for this result is the that this patch may have been closer in proximity to the vaporized cocaine, increasing the concentration on the outside. Another is that the buffering capacity of the artificial sweat may have been less than the bicarbonate buffer, resulting in a higher pH on the artificial sweat/artificial sweat patch membrane due to the presence of free-base cocaine and methamphetamine. It is also conceivable that one or more large particles of vaporized cocaine in the smoke settled on this patch. However, a more likely scenario would be afforded by results from the control solutions place in the box: vials of tap water, artificial sweat, and bicarbonate buffer. The vial containing the more acidic artificial sweat had 2.4 times as much cocaine as the bicarbonate vial and 6.1 times as much as the vial with tap water. Acidic media should help dissolve the vapor phase drug and increase its concentration. The increase in concentration may increase total diffusion through the outer patch surface.

To go through the outer membrane of the patch, drugs must be soluble in the membrane, and they must be removed from the interior surface. The normal removal mechanism is to be protonated by sweat, then dissolved in the sweat from the wearer thereby extracting the drug from the covering membrane into the interior pad. If the interior pad was not in contact with the

external membrane (or is dry), then it is predicted that drug diffusion would be reduced. To test this concept, a patch was constructed using the same membrane (3M Tegaderm dressings NDC 8333-1624-05) as the PharmChek Sweat Patch and a filter paper pad (Whatman #3) of similar size. In one patch a plastic mesh screen was placed between the filter paper and the membrane in place of the release layer of the commercial patch. This screen should still provide transport of water vapor yet prevent substantial contact with the outer membrane. After assembly, this modified patch was wet with artificial sweat inside and tested in the same manner as the sweat patch by exposing it to drug vapors (bicarbonate buffer was placed on the outside). This scheme reduced cocaine CFWO by 98% compared to a similarly constructed patch without the screen (inset in Figure 3). The difference between the design of the control and that of the commercial version is unclear. Methamphetamine was not taken-up by either the control nor the modified patch to any great extent. Nevertheless, CFWO was reduced by 50%. Alternative schemes of two polyurethane membranes (or other permeable membranes such as polycarbonate filters) with an air gap could also be used. Such a system would have the advantage of reducing flooding of the air gap that may occur during heavy exercise.

The current scheme to detect tampering is to see if the patch is still in place before it is removed and a visual inspection of the membrane for holes. Chemical detectors for pH and oxidation also should be included in any revised patch. These would indicate if the wearer injected bleach or base into the patch (intentionally or unintentionally). A single pinprick is very difficult to observe yet can still allow the introduction of foreign substances through pressure injection. Base would degrade cocaine to ecgonine, a compound not normally detectable by immunoassays or by GC/MS, and thus allow a cocaine user to escape detection. Heroin and methamphetamine would not be degraded to undetectable products and consequently users of these drugs would not generate false negatives.

Figure 3 - Vapor deposition of drugs. 9.4 mg crack cocaine and 4.7 mg of methamphetamine vaporized in 30x30x35 cm box. The inset shows the results of a modified patch with artificial sweat inside and bicarbonate outside.



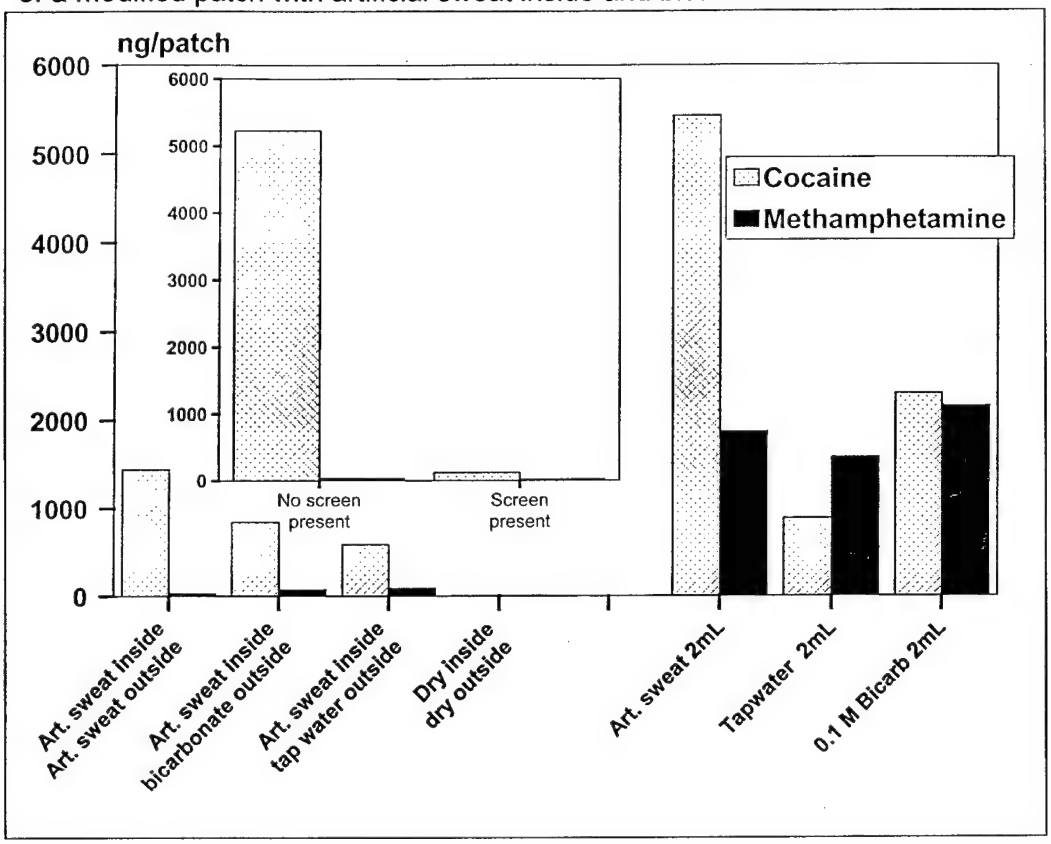
3.2 Contamination From WithIN (CFWI)

3.2.1 Skin contamination experiments

False positive interpretations may arise from prior presence of drugs on the exterior of the skin which are not removed by the cleaning process. CFWI is distinct from drugs permeating the skin (not covered by the patch), entering the blood stream, and being re-excreted by the sweat into the patch. Except in extreme cases of external contamination, this is unlikely to occur. Individuals administered physiologically active amounts of cocaine typically have microgram levels of benzoylecgonine in their urine yet have only nanogram amounts of cocaine in sweat patches worn during the cocaine use.[14] In applying up to 50 µg of cocaine to the skin of drug-free volunteers, no detectable level of benzoylecgonine was found in their urine (LOD < 3 ng/mL). Assume that application of 50µg of cocaine to the skin would have produced 3 ng/mL of BE in the urine. By a simple ratio, it would take an application of 248 mg of cocaine to the skin to reach the average BE level of 14900 ng/mL found in cocaine users.[31] Even fractions of this amount of cocaine would be readily observable if applied to the skin. Therefore, a positive sweat patch due to external contamination, penetration of the skin by the drug, and excretion into the sweat is unlikely.

The skin is "cleansed" before application of the patch using 70% isopropanol swabs. Previous

Figure 3 - Vapor deposition of drugs. 9.4 mg crack cocaine and 4.7 mg of methamphetamine vaporized in 30x30x35 cm box. The inset shows the results of a modified patch with artificial sweat inside and bicarbonate outside.



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The skin is "cleansed" before application of the patch using 70% isopropanol swabs. Previous research has shown that drugs can remain on the skin for several days after application and that 70% isopropanol is not the most effective solvent in removal of drugs.[17] Drugs containing positive charges likely bind to the proteins in skin in a similar manner as in binding to the proteins in hair, where ionic binding is thought to play a major role.[32] Thus, removal of drugs would be difficult because of this ionic binding. However, intensive sweating could assist in release of the drugs by hydrating the skin layer (facilitating diffusion) and providing cations to ion-exchange with the drugs bound to the proteins. Also, prolonged contact with the wet pad of the sweat patch could enhance drug transfer. Swabs employing acidic media containing water increases drug removal[17], consistent with this mechanism for binding. Isopropanol, being less polar than water, would neither hydrate the skin layer nor assist in breaking the ionic bonding of the drugs. Therefore, once applied to the skin, drugs could remain for several days due to ionic bonding, not be removed by "cleansing" with the isopropanol swab, and appear in the patch after sweat induced transfer, with greater concentrations occurring when sweating is greater.

To test the hypothesis that CFWI may be an issue, 10 µg of drug mixture were applied to approximately 9 cm^2 of skin of drug-free volunteers. Except in one experiment testing for drug equilibration, no patch was applied without at least one personal hygienic shower. In the real world, individuals shower or bathe daily, more or less, whether their skin has been contaminated with drugs or not. The number of showers as well as the thoroughness of personal hygiene would be expected to vary among individuals. Thus, some variability in results, caused by unequal removal of the drugs through personal hygiene, is inevitable. The amount of drug applied was arbitrary but not excessive considering that 300 ng of cocaine (as removed with a 70% isopropanol swab, maximum 30% removal rate) was found on the forehead of children living in a cocaine-use environment.[33] If drugs bind to skin though an ion exchange mechanism, it should be possible to saturate an area of skin with drug. It is possible that the 10 µg of drugs used in these experiments exceeded the capacity of the skin with the excess more easily removed during the personal hygiene. Future work will delve into the binding of drugs to skin in more detail.

3.2.2 Patches applied simultaneously, then removed sequentially

Figure 4 depicts an experiment where drugs were spiked on four areas of skin, hygiene was performed, and patches were applied simultaneously but removed sequentially. Figure 4 shows that CFWI can remain on skin even after normal showering, repeated skin cleansing with alcohol swabs, and even after wearing the sweat patch for two days (as evidenced by the post swabs). Repeated alcohol swabs of skin 15 hours after contamination showed 60 - 450 ng of all drugs applied. In addition, BE was observed in every alcohol swab prior to applying the patch, with concentrations of 42-64 ng. Relative to cocaine, BE concentrations ranged from 21-54%. Apparently cocaine can decompose to BE between placement on the skin and detection in the patch.

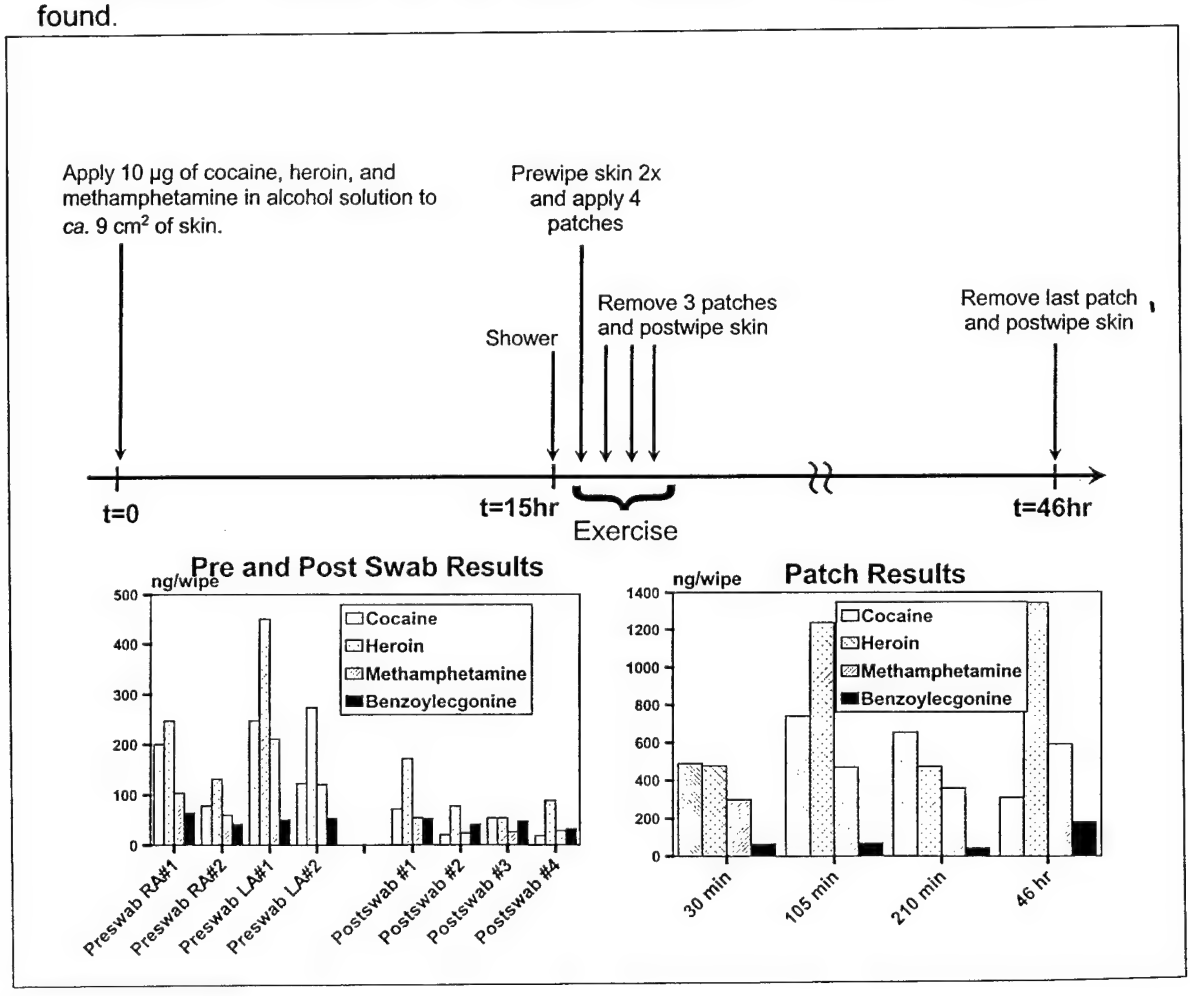
These results also reveal that, with exercise and active sweating, contamination by all three drugs (cocaine, heroin, and methamphetamine) can appear in the sweat patch within 30 minutes of its application. No conversion of methamphetamine to amphetamine was observed under the conditions of this experiment. However, BE appeared to increase relative to cocaine with time. As the interval of patch on the skin increased, the amounts of drug deposited in the

patch appeared to increase, generally, with BE highest in the 46 h patch (182 ng, or 60% relative to cocaine).

After the patch was removed, alcohol swabs of the skin (post swabs) under the 30 min patch showed the presence of cocaine, heroin, and methamphetamine. BE was present at 53 ng (73% relative to cocaine) due to degradation of cocaine. Even at 46 h, drugs applied were observed in the post swab.

This experiment shows that CFWI appears in the patch rapidly when the individual actively sweats. Both cocaine and BE appeared. Methamphetamine did not decompose or be metabolized into amphetamine. Alcohol swab "cleansing" removed some, but not all, of the drug contamination.

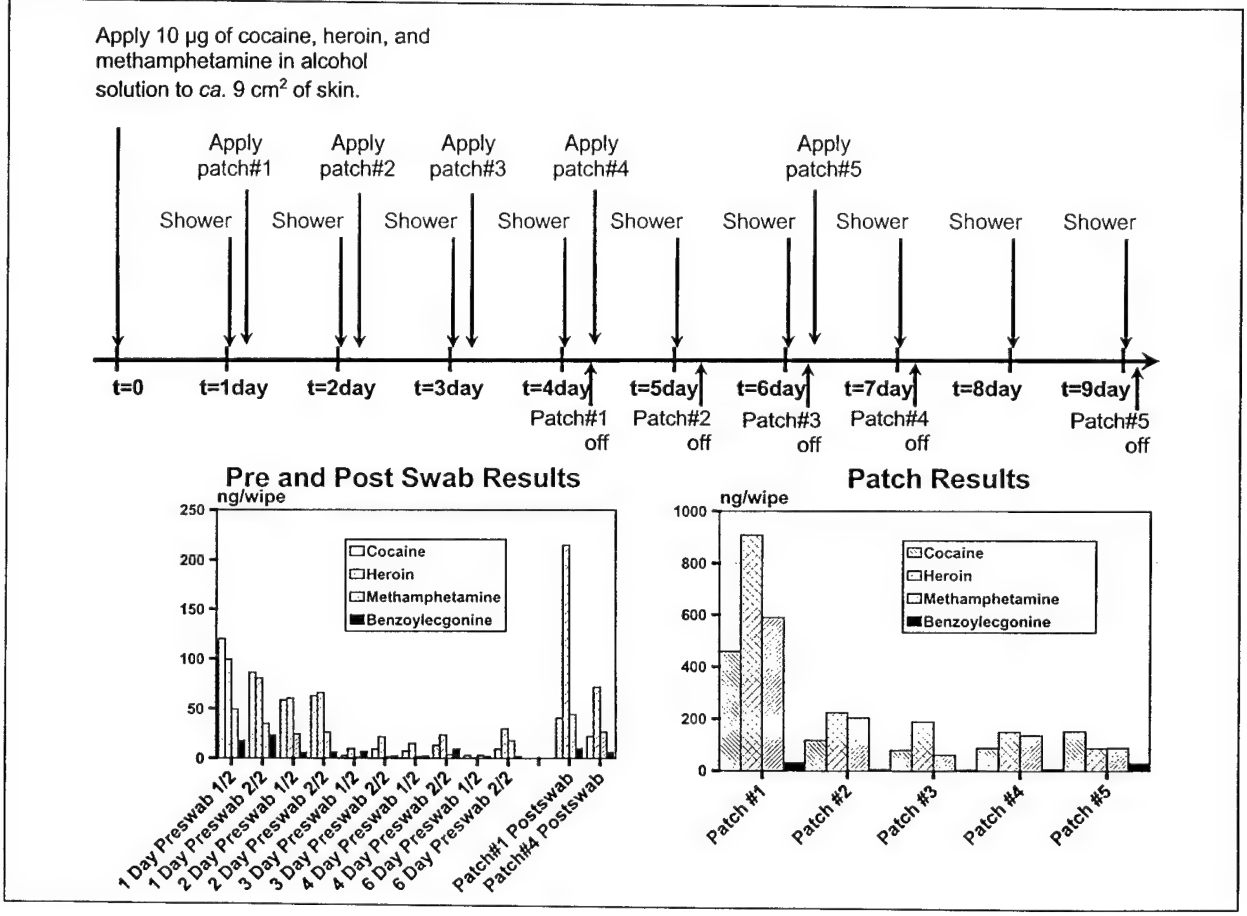
Figure 4 - Removal of patches at varying times. The top graph is a summary of the experiment and the bottom two bar charts the analysis results. No amphetamine was found.



3.2.3 Patches applied sequentially, then removed sequentially

Figure 5 depicts an experiment where drugs were spiked on five areas of skin and patches were applied at various times, days after the drug application, and with varying amounts of normal hygiene. All sweat patches showed CFWI. Sweat patch concentrations of all drugs applied to the skin generally decreased over time, with a few data points showing variability from this trend. Even when the patch was applied seven days after skin contamination with drugs, cocaine, BE, heroin, and methamphetamine were deposited in the pad. Sources of variability may include the extent of normal hygienic cleansing, the placement of the sweat patch over the contaminated area, and the effects of exercise on active sweating.

Figure 5 - Application of patches at varying times. The top graph is a summary of the experiment and the bottom two bar charts the analysis results. No amphetamine was found due to degradation of methamphetamine.



Skin swabs taken just prior to patch applications (pre-patch swabs) trended downward as more time elapsed since drug contamination was applied to skin. On day 1, the highest concentrations were observed. By day 6 (7 days after drug was applied), only one pre-patch swab contained detectable quantities of drugs. No production of amphetamine from methamphetamine was observed.

Concentrations of drugs decreased between the post-swab after patch #1. (Several post-patch alcohol swabs were lost.) These results show that it is possible for an individual to be externally contaminated with these drugs on one day, perform normal hygienic washing for at least six

days, cleanse the skin *twice* with 70% isopropyl alcohol swabs, and still test positive for cocaine, BE, heroin, and methamphetamine in the sweat patch.

3.2.4 Stability of drugs in the patch

Drugs may not persist inside the patch for two reasons: (1) the drugs may be degraded by enzymes present in sweat, bacteria inside the patch, or the humid environment, or (2) the drugs may equilibrate with the skin, passing from the patch back into the skin, eventually through the skin into the body, and be eliminated. To test the latter possibility, patches were spiked with 500 ng of drugs, allowed to dry, and placed on the skin. Controls areas of the skin were also spiked with 500 ng of drugs, allowed to dry, and immediately covered with another set of patches. In this manner, both transfer of drugs from the skin to the patches and transfer of drugs from the patches to the skin could be measured. If equilibrium were reached, then all the patches should have the same amounts of drugs. The percentage of drugs remaining in the patches and transferred from the skin are given in Table 2. As indicated, only about a third of the drug is transferred to the patch from the skin. However, once on the patch, less is transferred from the skin to the pad. The percentages given in Table2 are not corrected for the recovery of the drugs from the patch. However, this is partially accounted for in the extraction procedure by adding the internal standards to the patch before extraction.

Table 2 - Percent transfer of drugs to/from the patch and skin. Patches were done in duplicate and the results averaged.

	Cocaine	Heroin	Methamphetamine
Spiked on skin (%CV)	33% (0.5)	30% (3.8)	32% (2.2)
Spiked on patch (%CV)	60% (1.7)	64% (1.8)	46% (1.4)

3.3 Lactic acid results

We observed that some individuals did not transfer as much drugs to patches as others even though their skin was contaminated to the same extent. Because the patches were applied after hygiene, one explanation may be variable hygienic drug removal. An alternative explanation could lie in the observation that the individual who transferred the least drug also did not actively exercise. Other (occlusive) patch designs allow sweat volume to be measured by weighing the patch, but this would not work with this (nonocclusive) patch because water transpires though the covering. Thus a surrogate of sweat volume was needed. Because lactic acid is present in sweat, its concentration was measured to estimate the amount of sweating. Initial results show only a poor correlation with lactic acid and drug transfer results (Table 3).

Table 3 - Lactic acid and drug concentrations for two individuals. Individuals were spiked with 500 ng of cocaine, heroin, and methamphetamine, the patches were applied, and worn for 3 days. Subject 2 exercised heavily whereas subject 1 only exercised lightly.

	Cocaine	Heroin	Methamphetamine	MDMA	Lactic Acid
Subject 1 - RA	202	141	365	181	431
Subject 1 - LA	228	196	417	224	800
Subject 2 - RA	294	353	297	250	1636
Subject 2 - LA	376	436	320	311	1573

It is not known what mediates the transfer of drugs from the skin to the patch (sweat volume, sweat pH, or ions presence could be possibilities). Lactic acid concentrations are higher in resting sweat and lower in exercise induced sweat (although the volumes are greatly different). Because the patch collects both types of sweat, the marker provided by lactic acid may be clouded. For example: an individual may not exercise, his/her patch would be dominated by insensible sweat, and a high lactic acid concentration reached compared to an individual who exercises heavily, always saturating the patch (with mainly water), and having his/her patch dominated by exercise induced sweat with low lactic acid concentrations. The exercising individual may have a similar lactic acid concentration in the patch compared with the resting individual yet the drugs would have had a greater opportunity to be transferred to the patch due to the aqueous environment being constantly present.

3.4 Sources of drug contamination

Potential sources of drug contamination are plentiful. Cocaine in particular and also methamphetamine, are found on paper currency.[34],[35],[36] Although drugs on currency are hard to transfer to the skin, they can transfer if the skin is moist.[37] This indicates the ease that drugs can spread through the general environment. Likewise, individuals whose environments are predicted to contain drug contamination show higher levels of drugs on their skin.[33] Other reports show that the clothing of drug abusers retain opiates [38] and cocaine metabolite.[39] Touching the patch with one's hand is a natural reaction to materials on the body. Also, some court officers consider it a violation if the patch peels-off. Thus, intentionally pressing on the patch to keep adhered to the skin could also transfer drugs to the surface from the hands. Alternatively, wearing a close-filling undershirt, contaminated with as little as microgram quantities of these drugs, (above the patch), and sweating could transfer drugs to the surface of the patch. The laboratory studies show that the potential for external contamination of skin (CFWI) as well as contamination of the patch membrane (CFWO) can occur and generate false positive results. The exact percentage and degree of drug contamination in specific environments is generally not known. Future research on this subject could provide a basis for probability correlations.

3.4.1 Presence of metabolites and degradation of methamphetamine by bleach.

To the extent that drugs must pass through the human body to produce metabolites, metabolites can increase the reliability of a positive result. Unfortunately, for cocaine the major metabolite, benzoylecgonine, is present to a small extent in street-grade cocaine[40] and

appears to be produced by cocaine degradation on the skin. In contrast, amphetamine is the major metabolite of methamphetamine and is less likely present in illicit methamphetamine preparations. Nevertheless, amphetamine is sometimes sold as methamphetamine and thus may contaminate the environment. Contamination may also come from the sweat of prior use. Because the individual being tested may still reside in the same location, wear clothing, or contact other drug users, this contact may put that individual in proximity to metabolites generated from other people or at prior times. Contact with metabolites may be ruled out based on the circumstances of the subject's environment but contact with the parent drug could still be a possibility. Could metabolites be generated in vivo on the skin? Cocaine is known to be unstable and degrade to benzoylecgonine in base. In contrast, methamphetamine is relatively stable and thus the presence of amphetamine may be a marker that the drug was excreted from the human body rather than entered the patch from the outside. In the present of strong oxidants such as sodium periodate, 1-2% of methamphetamine is converted to amphetamine.[41] An individual could have CFWI or CFWO of pure methamphetamine, come in contact with bleach (in a swimming pool for example), and have a small amount of the methamphetamine be converted to amphetamine. To test the stability of methamphetamine to hypochlorite oxidation, methamphetamine was exposed to increasing amounts of commercial bleach; up to 5.6% of amphetamine was generated (Table 4). Higher ratios of amphetamine to methamphetamine in the patch could indicate that the individual used methamphetamine, as long as the presence of amphetamine in the environment can be discounted.

Table 4 - Oxidation of methamphetamine with commercial bleach

Amount of bleach (µL)	% Bleach in final solution	Amphetamine/ methamphetamine ratio (%)
5	0.026	1.6
10	0.05	3.1
20	0.11	4.4
30	0.16	5.6

3.5 Criteria for detection of contamination

Of the two possibilities for a false positives, CFWI and CFWO, CFWI is the more likely scenario because less drug must be present to cause a false positive. One way to detect CFWI is to save the single swab used to clean the skin and only analyze it if questions arise about the results. If possible, the swab should be modified to include a mild acid with the 70% isopropanol. Based on our results with "cleaning" using swabs containing 70% isopropanol, the swabs generally have 10% or more of the value eventually found in the patch (see Figure 5). Therefore, two criteria may be suggested to reduce prior CFWI. The skin swabs used for "cleaning"must be <10% of patch results for results to be acceptable (no safety factor) and all must be above the LOD. For example: if the LOD for the swabs were 5 ng/swab, then the cut-off level for the patch could be no lower than 50 ng/patch to allow the possibility of detection of drugs in the skin swab. If the skin swab was greater than 10% of the patch results than the results could come from drug use or drug exposure prior to wearing the patch (although contemporaneous use or intentional contamination could not be ruled out). Saving and

analyzing the skin swab with the current sweat patch design may reduce or provide added information concerning CFWI.

4. Conclusions

Problems with CFWO and CFWI can occur with the present design for the sweat patch. Redesign of the patch with an air gap should reduce CFWO. Saving the swabs used for "cleaning" the skin (with possible inclusion of mild acid in the isopropanol) for testing can improve interpretations, if any positive results are questioned. Following up an individual who denies drug use with frequent urine tests may also be one response to both CFWO and CFWI. Appropriate care should be taken in interpretation of positive results from a sweat patch test until more research is conducted.

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